AUG 12 1997

Ref: 97-F-1164

Dr. Chris Dickey
[redacted]

Dear Dr. Dickey:

This responds to your June 2, 1997, Freedom of Information Act (FOIA) request addressed to the Defense Advanced Research Projects Agency (DARPA). Our June 27, 1997, interim response refers.

DARPA was unable to locate any documents concerning "human cellular platforms used for biological warfare therapy," as you requested. You requested this information from the DARPA Immediate Countermeasures Division. DARPA advises that this division does not exist, nor does DARPA have a research program for human cellular platforms used for biological warfare therapy.

DARPA does have a Biological Warfare Defense (BWD) Program, in the Defense Sciences Office, which includes an Unconventional Pathogen Countermeasures (UPC) Program. Within the UPC Program, DARPA is employing a variety of strategies which feature the red blood cell and mesenchymal stem cells as platforms for biological warfare defense. They are specifically: 1) HeteroPolymer-Erythrocyte and Protective Ensembles on Erythrocytes for pathogen defense and 2) Mesenchymal stem cells as a platform to provide within the body automatic immunization against a variety of pathogens.

DARPA has provided the enclosed documents for your information. The enclosed briefing slides were used in DARPA's presentation of the BWD program and explains the overall DARPA BWD program, including "Medical Countermeasures" such as the "Heteropolymer Mediated Binding of a Target Pathogen to Red Blood Cells" and "Mesenchymal Stem Cell Differentiation." Also enclosed is a media package of three published articles and hard copies from the DARPA web site that relate to the BWD program. The DARPA web page is at www.darpa.mil, and additional information on the UPC program can be obtained at www.bwd.org/upc/.

Should you deem this no record response to be an adverse determination, you may appeal this finding by offering justification to support an additional search effort. Any such appeal should be received in this Directorate within 60 calendar days of this letter's date. Our address is: Directorate for

#884

Freedom of Information and Security Review, Room 2C757, 1400 Defense Pentagon, Washington, DC 20301-1400.

There are no charges for processing this request in this instance.

Sincerely,

[redacted]

SIGNED
A. H. Passarella
Director
Freedom of Information
and Security Review

Enclosures:
As stated

Prepared by jhogan:7F1164L1:8/11/97:DFOI:X74026:gr/pk__yl__wh__

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DARPA Biological Warfare Defense Program

Program Overview

Briefing slides

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Why is Biological Warfare Defense a Very High DARPA Priority ?

- Troops, ports, airfields, supply depots, etc. are vulnerable to biological attacks
- A number of countries have developed or are developing offensive biological capability
- Most likely first use will be against population centers of ours or our allies
- Small demonstration and threat probably adequate to immobilize national will with panic unless reasonable defenses are available

Why is Biological Warfare Defense a Very High DARPA Priority?

This new initiative is motivated by the threat of biological warfare, and the critical need to develop broad strategies to counter the threat.

It is becoming widely recognized that biological warfare is a threat with unlimited potential. In the wake of the Gulf War and the activities of the Aum Shinrikyo in Japan, recent press reports have noted the interest of several countries and terrorist organizations in developing biological weapons. Of great concern is the enormous mismatch between these potential threats and current capabilities for dealing with them. As interested states and terrorist organizations become more adept in applying biotechnology to the design of biological weapons, this disparity can only increase, with potentially disastrous consequences. At the same time, new natural infections, with similar underlying mechanisms of disease, will continue inexorably to emerge. The great challenges presented by these unpredictable threats will require innovative, even revolutionary, new strategies. DARPA believes that partnerships with industry and the research community will be essential for meeting these challenges.

The main objective of DARPA's Biological Warfare Defense Program is to protect all U.S. military troop operations from biological attack. This includes protecting supply routes through ports and air fields. We have an even greater concern that terrorists will use biological warfare agents against U.S. or Allied-Nation population centers. In the scenarios we imagine, it is not necessary to have achieved a 100% effective attack in order for the attacker to have achieved his objective. And any adversary may now easily acquire and utilize effective biological warfare capabilities to serve his purposes.

DARPA Biological Warfare Defense Program

Goal

Eliminate the threat of biological weapons (including bacterial, viral, and bioengineered organisms) as a factor in the planning and conduct of US military operations

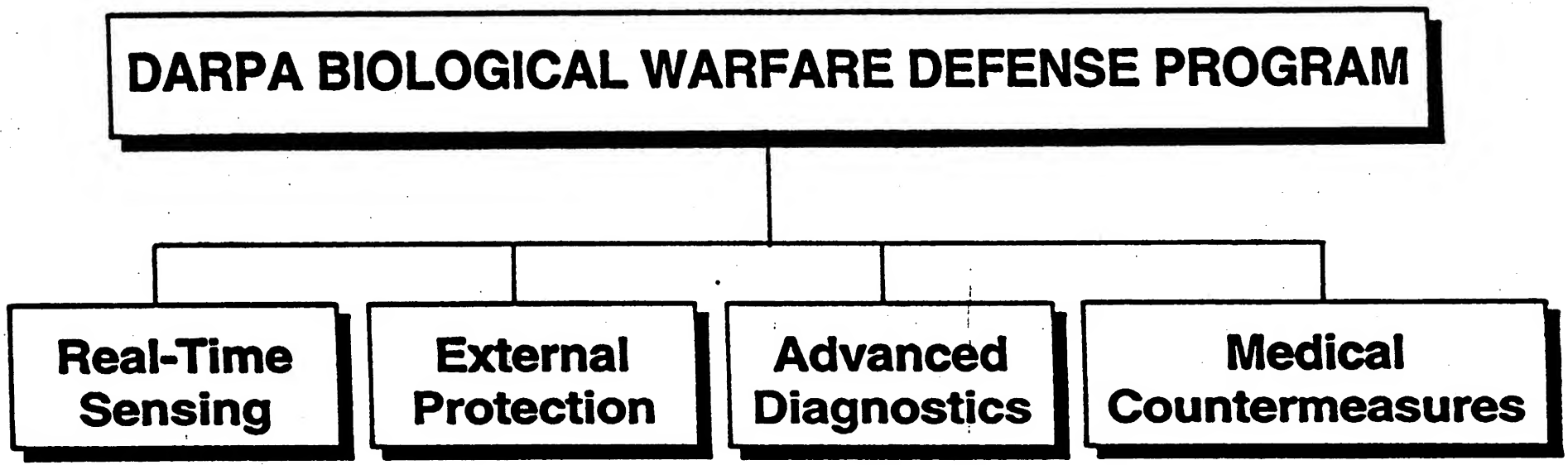
DARPA Biological Warfare Defense Program Goal

DARPA, the Defense Advanced Research Projects Agency in the Department of Defense, is seeking partnerships with the research community and the biotechnology and pharmaceutical industries to develop innovative new treatment, prevention, and diagnostic strategies for biological warfare threats.

DARPA has established an ambitious goal for itself with the formation of its Biological Warfare Defense (BWD) Program: Undermine the utility in warfare of the use of all biological agents — pathogens and toxins.

In general, the program strategy is intentionally multi-agent, rather than targeted to individual pathogens, leveraging research and development in areas such as host-pathogen interactions and novel infectious disease therapeutics. DARPA is projecting substantial funding for this high-priority initiative, and approximately $30 million has already been allocated as a first installment in FY 1997.

DARPA BIOLOGICAL WARFARE DEFENSE PROGRAM



Supporting Technologies

- Informatics
- Microfluidics
- Advanced Mathematics
- Combinatorial Chemistry

DARPA's Biological Warfare Defense Program

The DARPA biological warfare defense program has four major thrusts: Real-Time Sensing, External Protection, Advanced Diagnostics, and Medical Countermeasures. Four underlying technology development areas support these thrusts. Let us take these roughly in the sequence in which the stages of a BW attack might unfold:

Real-Time Sensing: A wide variety of sensors distributed throughout the region of interest (including being located directly on personnel), along with integrated, miniaturized sample processors and analyzers, form the means by which samples are continuously taken from the environment and immediately assayed. Data pertaining to this collection and identification process is relayed to regional and local commanders, also on a real-time basis.

External Protection: Upon registering a positive indication of a bioagent's presence in the battlespace, an immediate order is given to troops in the affected area to don external protection (e.g., protective suits and/or masks). DARPA will be funding concepts that could enable these suits and masks to be self-decontaminating.

Advanced Diagnostics: If external protection could not be donned in time, was not available to everyone in the area, or was, for other reasons, not effective, and bioagent exposure takes place, illness presumably then sets in among the military and/or civilian population, and advanced diagnostics come into play. These diagnostics would include, for instance, medical detection systems capable of identifying a wide variety of pathogens in body fluids (saliva, sputum, or blood).

Medical Countermeasures: Medical countermeasures may be taken before, during, or after exposure to the bioagent(s) — overarching all other elements of the program. We discuss the advanced preventive and therapeutic facets of this activity in greater detail in a second section of this presentation.

Supporting Technologies:

Informatics — the collection, processing, management, interpretative analysis, and display of widely differing forms of information to the military user — is a traditional expertise of DARPA. We are taking many past developments and are applying them to BW.

Microfluidics is a broader DARPA program looking at the ability to handle very small quantities of fluids on microchips. Some of that work is highly relevant to the biological warfare defense program in support of sensors and other diagnostics.

Advanced Mathematics, another traditional strength of DARPA, is focused on signal processing. We are going to apply this capability in the BW arena to the "data mining" of genomes and to determining what chemistries are reactive with different pathogens.

Combinatorial Chemistry is directed at the production of better probes for real-time sensors, advanced diagnostics, development of better therapeutics for BW medical countermeasures, and denaturing pathogens in the external protection program.

Information Problems

- Managing BW attack is very complex; requiring knowledge not usually available in real-time
- Lack of access to the "few who know"
- Information overload when it comes, not cogent or organized to meet the need
- What to do is not well structured (correct protocols)

Information Problems

Informatics is an area of traditional strength at DARPA. This chart features several areas where we feel DARPA's Informatics expertise can be applied to the problem of Biological Warfare Defense. BW attacks can be so complex that it may actually be quite difficult even to ascertain that one has taken place. Part of a BW attack's complexity lies in confirming its occurrence: information about people arriving at medic stations or hospitals with flu-like symptoms must be cross-correlated, because many BW agents express such symptoms during the first 24 to 48 hours after exposure (see discussion below).

Once the fact of an attack has been established, individual domain experts in BW defense, treatments, and countermeasures must be contacted immediately so they can issue orders on the kinds of protocols to be followed. These individuals are likely to be few in number, and reaching them immediately with the available information is critical.

The information exchange can very quickly become overwhelming, since many of the first responders to military situations are likely to be medics who are highly trained in stopping bleeding (the primary injury on a battlefield). Military medics are not, however, extensively trained to deal with exposure to all varieties of BW agents. They *are* trained to identify that a biologic attack has taken place and to request information on what to do, e.g., whether a patient can be contagious in an aerosol form — of considerable importance as he is moved into the upper echelons of medical care. The same can be said of civilian emergency agencies responding to a terrorist attack in a city.

First responders to these situations need new technologies that are probably quite foreign to their normal practice. If civilian police, fire, and/or local hospitals responding, they will need information in a ready-to-use form — *not* one requiring expert training.

This brings us to the final point of correct protocols. We must make available simple, clear information on performing a diagnosis and, once done, how to proceed with treatment.

DARPA Biological Warfare Defense Program

Medical Countermeasures

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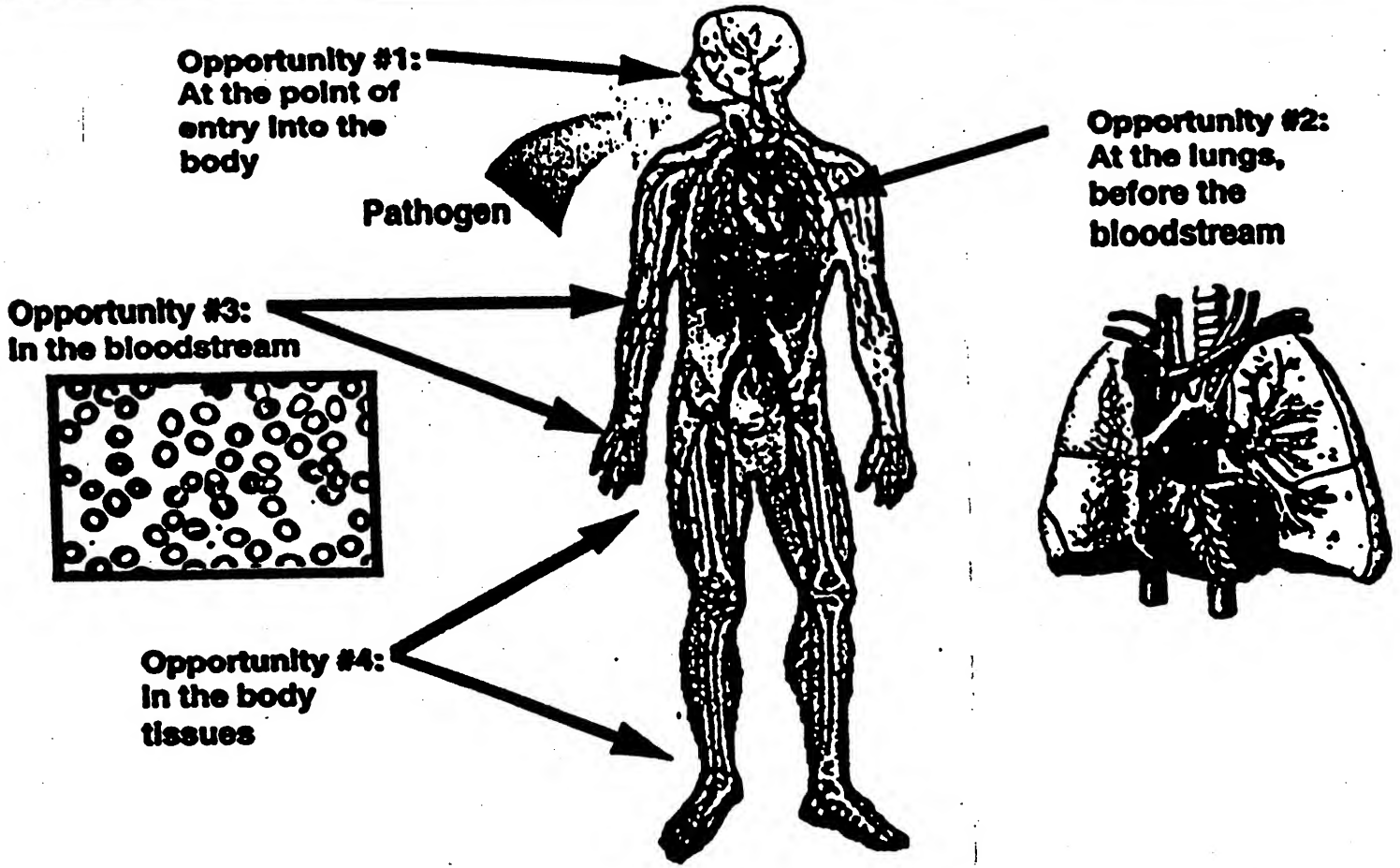
Defense Against Pathogen Attack: a Multi-Level Approach



Defense Against Pathogen Attack: a Multi-Level Approach

The safety of our troops requires that we not rely only on a single defense mechanism against lethal pathogens. Therefore, the DARPA Medical Countermeasures Program is based on a multi-level approach to provide the required pathogen defenses.

Earlier, we mentioned external protection. These technologies fall into two categories and serve as the first line of defense against pathogens: (i) materials that can be spread on the skin to provide protection, or (ii) improved protective clothing and masks to provide barriers outside the body. Now, let us turn to identifying the locations in the body where the pathogen can be attacked. There are four levels of opportunity where an effective pathogen defense can be mounted:

(i) At the point of entry: The first opportunity to defeat the pathogen at its point of entry into the body is via the lungs or the gastrointestinal track. Exposure to most pathogens will be through inhalation. Contaminated food or water could also provide a pathway via the gastrointestinal track. In the future, some pathogens may be able to pass through the skin transdermally or transcutaneously.

(ii) At the lungs, before the bloodstream: When DARPA first started this program, we had some concerns that trying to mount too fierce a defense in the lungs would induce edema or ARDS. This would be tantamount to winning the battle and losing the war: neither the pathogens nor the patient survives the regimen. However, the progress observed over the past year this continues to be an area in which we may wish to pursue those approaches that offer the highest likelihood of sustaining the patient while defeating the pathogen.

(iii) In the bloodstream: Next, pathogens travel to the bloodstream. We are developing programs designed to defeat the pathogen at this stage.

(iv) In the body tissues: DARPA is developing promising technology to attack pathogens once they have arrived in the body tissues.

Medical Countermeasures

Program Goals:

- Develop agent specific, advanced therapeutics with broad spectrum application
- Target common mechanisms of pathogenesis and functions or structures shared by groups of pathogens
- Modulate the human biological response to pathogens

Medical Countermeasures

Our program goal is comprised of two major thrusts: one is the multi-agent (yet, agent-specific) approach, and the other is a common pathways approach.

In the multi-agent/agent specific thrust, the approach will be targeted to a specific pathogen, but it is applicable to several different pathogens. For example, an approach may be used to develop therapeutics against twenty different pathogens. Twenty different pathogens may require twenty different versions of this therapeutic, but the *approach* to develop the therapeutic would be applicable to all.

The common pathways approach has two parts. The first identifies the details of pathogen behavior (either in how they sustain their own life or cause mayhem within the body by turning those mechanisms off). Alternately, diseases — especially the filoviruses, Ebola being the most notorious — can induce a response within the body that causes damage to the body's own tissues. The body's response to the pathogen actually leads to death; not the direct action in the pathogen itself. The most lethal effects of certain classes of pathogens can most effectively be countered by altering the way the human body responds to them.

Medical Countermeasures Program

Thrust 1

Agent-Specific

Therapeutics based on:

- Heteropolymer "decorated" red blood cells
- Stem cells
- Dendrimers/multivalent binding structures
- Invasive (intra-cellular) antibodies
- Rapid Immunization
- Engineered T cells for enhanced immunity

Thrust 2

"Common Mechanism"- Multi-Agent

Therapeutics based on:

- Red blood cells with surface-bound enzymes to inactivate pathogens
- Blocking Type III secretion mechanisms in bacteria
- Identifying pathogen genes required for infection and RNA-protein interactions required for pathogen survival
- Blocking virus interaction with required host factors
- Broad-spectrum anti-viral chemokines
- Developmentally regulated (gestational) products as a source of novel therapeutics

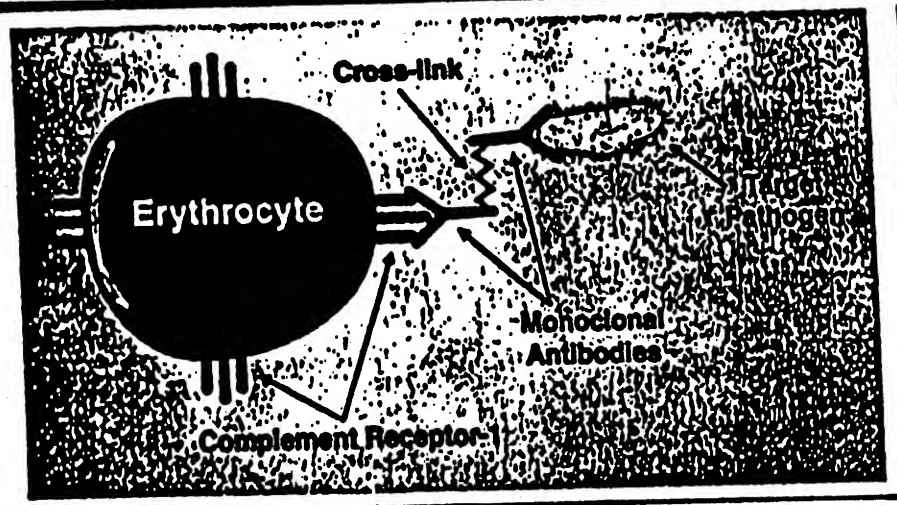
Medical Countermeasures Program

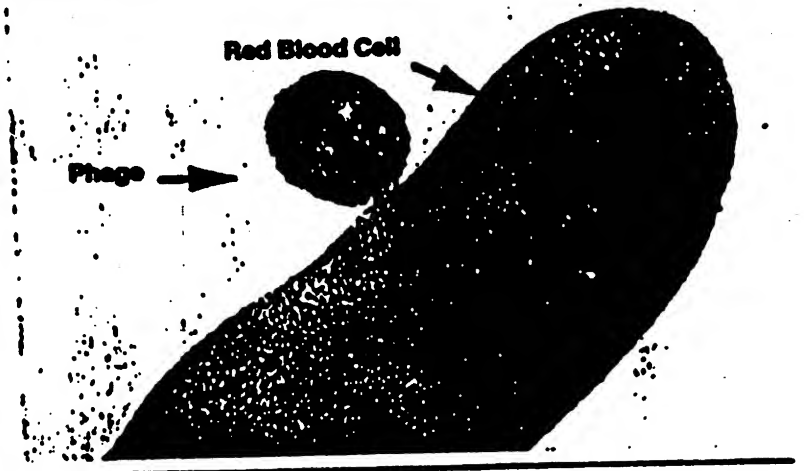
To amplify the two thrusts of the DARPA Medical Countermeasures Program introduced in the previous chart:

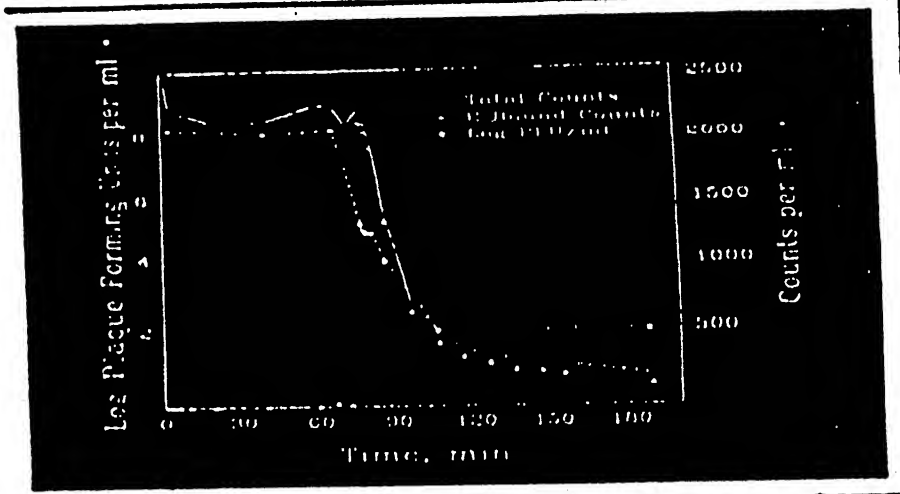
Thrust 1, "Multi-Agent, Agent-Specific" Approach: although one must "know his pathogen," the approaches being developed can be applied to multiple pathogens, and

Thrust 2, "Common Pathway" Approach: identifying common pathways shared by broad classes of pathogens, leading to the development of therapeutics that can simultaneously attack and neutralize broad classes of pathogens.

Heteropolymer Mediated Binding of a Target Pathogen to Red Blood Cells







Conclusions and Implications

Demonstrated greater than million times reduction of virus from bloodstream in 1 hour

Bound heteropolymers have a > 2 day lifetime in the circulation and may be useful for short term passive immunization

Early experiments show no toxicity and minimal immunogenicity

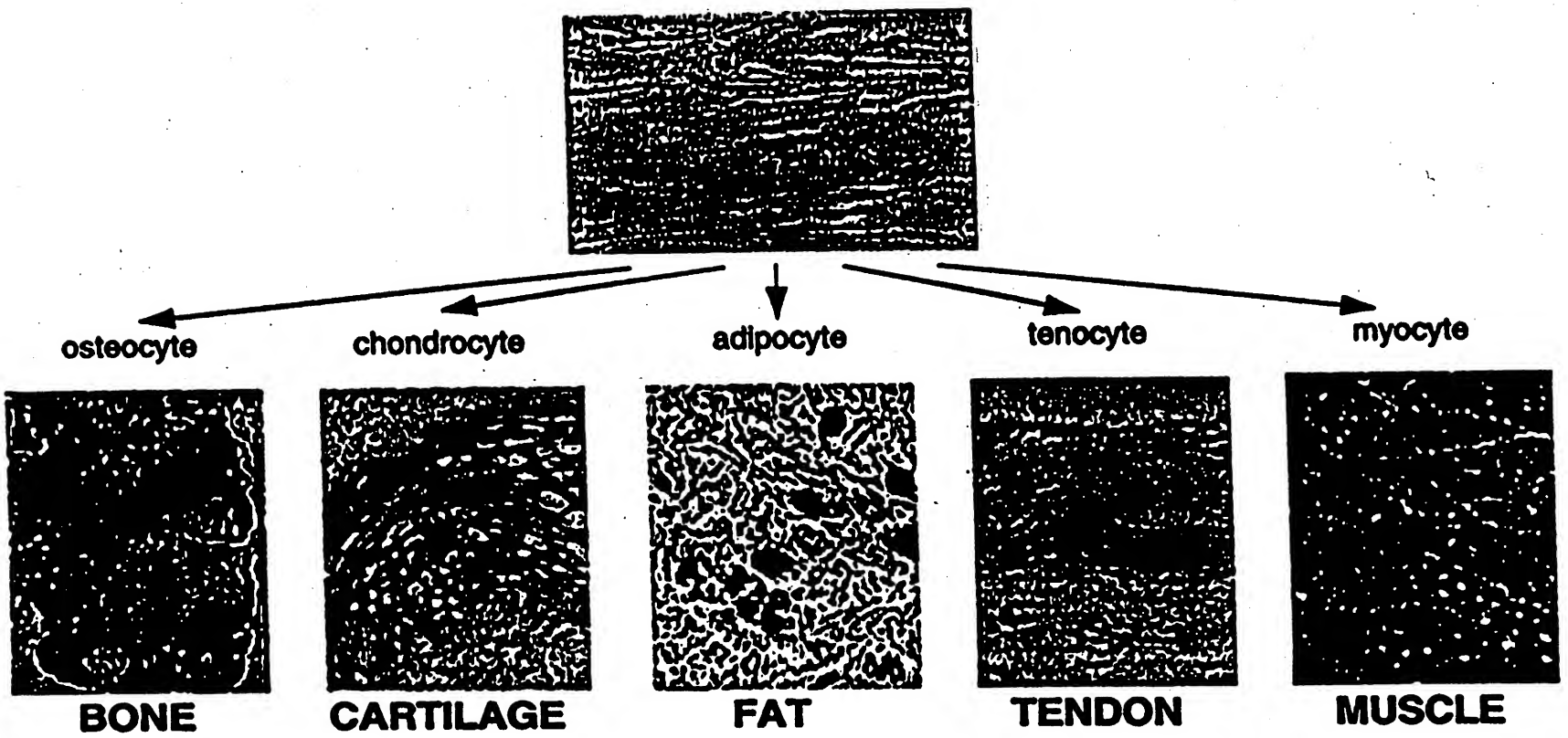
DARPA

Heteropolymer Mediated Binding of a Target Pathogen to Red Blood Cells

We have had some early success with the heteropolymer-decorated red blood cells. This project was started in May of 1996 at the University of Virginia under Professor Ron Taylor. Taylor and his colleagues developed a heteropolymer that functions on the one end to connect to the CR1 site of the red blood cells, while the other end is tailored to the specific pathogen. The idea is to "decorate" red blood cells with this heteropolymer. These decorated red blood cells "patrol" around the vascular space; and when they come in contact with the target pathogen, the pathogen becomes linked to the red blood cell. When these red blood cells pass through the liver or spleen, the heteropolymer is clipped at the CR1 site and releases the red blood cell back into the bloodstream undamaged. Meanwhile, the pathogen is delivered to a location where the body can destroy it. One remarkable feature of these early results demonstrates that *the red blood cells are able to continue performing their oxygen-carrying functions, and a clotting cascade is not induced.* There is no appearance of toxicity, no large-scale immunogenic response.

These experiments have taken two different approaches. In one approach, the protective heteropolymer is injected directly into the bloodstream. After a period of 2-5 days, a direct challenge is made with the virus, i.e., the virus is directly injected into the bloodstream. In these tests, with less than one percent of the red blood cells decorated, the heteropolymer-tagged blood is able to reduce the viral load by a million-fold in one hour. In the second approach, the virus was introduced into the bloodstream, and then the heteropolymer was injected. The heteropolymer correctly attached to the pathogen and tied them to the red blood cells — and the protective effect was rendered. This research is still preliminary, but the ability to filter out viral loaded or bacterialized pathogens from the body's bloodstream is extremely exciting.

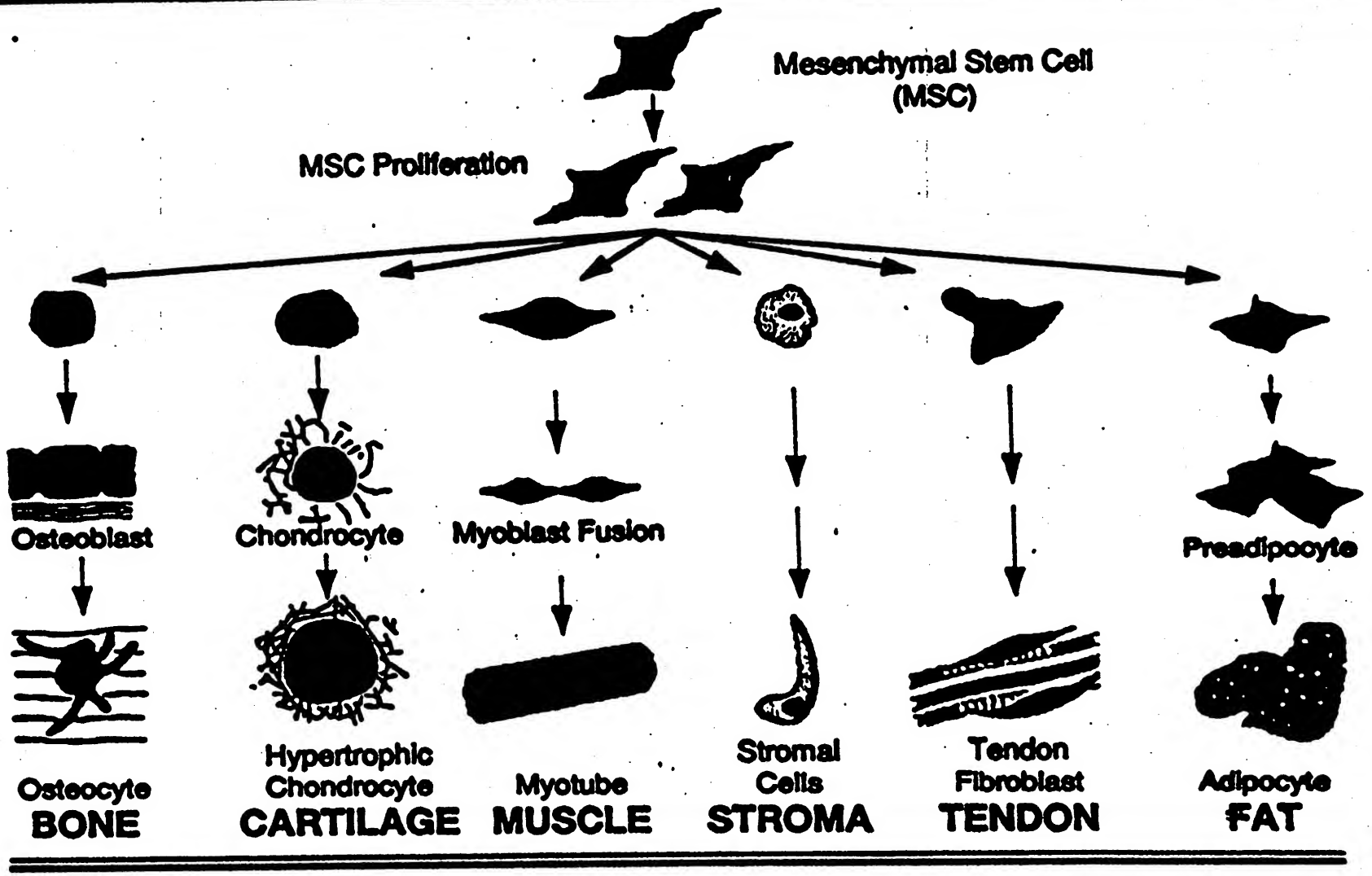
Mesenchymal Stem Cell Differentiation



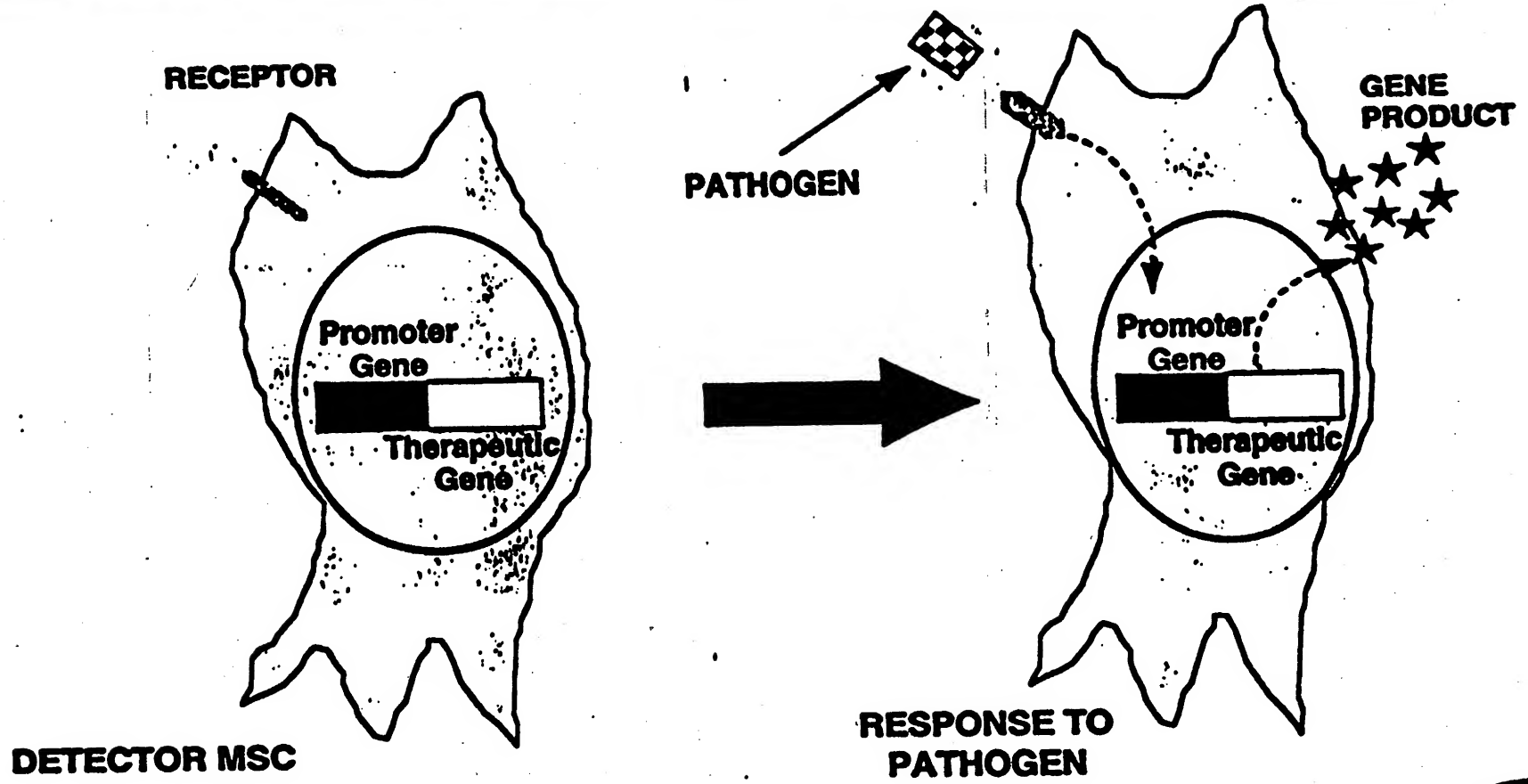
Mesenchymal Stem Cell Differentiation

The MSC research is in its earliest stage. Funding was started in May, 1996. Several questions remain unanswered, foremost "Can the MSC's ability be retained as it differentiates into its daughter cells (the muscle, tendon, fat type cells in the body)?"

The Mesengenic Process



Modified Mesenchymal Stem Cells Detect Pathogens and Release Products



Modified Mesenchymal Stem Cells Detect Pathogens and Release Products

DARPA is also funding research in mesenchymal stem cells (MSCs). Stem cells are the totipotential cells capable of producing a variety of tissues in the body, bone, cartilage, fat, tendon, and muscle. In this research, some of these mesenchymal stem cells are being modified to have surface receptors designed for specific pathogens. When that pathogen is detected, part of the cell's DNA is turned on to produce a therapeutic. This therapeutic is basically a gene protein product targeted to kill the pathogen. The advantage of this approach is clear: no longer must the body be flooded with the drug; this approach enables the drug to be produced in the body at the precise locations where the pathogens are encountered.

Medical Countermeasures Program Strategy

Part of DARPA's program strategy in medical countermeasures development is to fund basic research that will allow us to understand and develop therapeutics that demonstrate, in a proof-of-principle, that they are efficacious in attacking broad classes of pathogens. To address specific Biological Warfare agents, we will fund work at facilities such as USAMRIID, where actual bioagents are kept, to determine if the therapeutics are effective in animal models. If this approach works, the therapeutics will target not only third world diseases (i.e., encompassing most Biological Warfare agents), but also members in the class of first world diseases with economic potential. At this point, either with or without our co-funding, the pharmaceutical industry would take those drugs and proceed with the clinical testing required and the full development process.

In addition, while developing the therapeutics, we will explore the issue of making our therapeutics available to those aid agencies that help in world crisis situations involving natural outbreaks of currently lethal diseases that have no known treatments. Even though these are not truly designed for clinical trials, there is important information on whether these therapeutics are working against agents. A graphic example of this is the Ebola outbreaks, against which we currently have no effective therapeutics.

Our overarching approach is that DARPA will provide the thrust and the biotech industry and pharmaceutical industries will take over these products to commercialize them for their own purposes. DoD will then be able to procure them through normal commercial routes for use by our troops involved in conflicts or terrorist actions where BW might be present.

DARPA web

Overview of the Defense Sciences Of

The Defense Sciences Office (DSO) is the most diverse office within DARPA not only in mission but in character. Unlike the "systems offices" and the other "technology" offices, each of which has a defined area of concentration and expertise, DSO is designed to be the technological conscience of DARPA. DSO's mission is to identify and pursue the most promising technologies within the basic science and engineering research community and develop them into new DoD capabilities. DSO personnel draw on expertise from many elements--industry, university, government laboratories, small business, and individuals. The scope of the work funded under DSO spans the research and development spectrum from idea conception to actual production.

Currently, the DSO portfolio is composed of four general areas all striving to make the warfighter more maneuverable, survivable, efficient and affordable. These are: Advanced Materials Technology, Applied and Computational Mathematics, Advanced Biological and Medical Technologies, and Design and Manufacturing.

Advanced Biological and Medical Technologies

DARPA is applying the latest advances in medicine, medical technology, and microbiology to augment the warfighters' capabilities.

The effort has three major programs in the area of advanced biological and medical technology: combat casualty care, unconventional pathogen countermeasures, and biological warfare defense.

Combat Casualty Care

The emphasis of the Combat Casualty Care program is to develop technology to reduce by 30-50% the mortality of current far-forward casualties. The program applies recent advances in high-rate information sensing, signal processing, and transmission to bring trauma care to the injured soldier on the battlefield. This combat informatics thrust exploits existing and emerging technologies to develop a battlezone electronic patient record for combat casualty care. A prime example is the medic's associate software system that provides decision to far-forward caregivers.

A principle technology focus of the Combat Casualty Care effort is in the area of advanced far-forward non-invasive diagnostics. This includes the development of a personnel status monitor for continuous measurement of individual physiologic vital signs, portable blood chemistry units, portable body imaging devices, and exploratory work in advanced telemedicine and telesurgery. Additional emphasis is placed on the development of technologies, more immediate medical and surgical intervention, advanced simulation to improve the training of battlefield health care providers and to ensure skill currency, and the development of an advanced health care information infrastructure to support the entire combat trauma care technology.

Unconventional Pathogen Countermeasures

The intent of the Unconventional Pathogen Countermeasures Program is to develop and demonstrate defensive technologies which afford the greatest protection to uniformed warfighters, and the defense personnel who support them, during US military operations. While no defense may stop a determined adversary from unleashing biological weapons, a sufficiently robust array of pathogen defenses and countermeasures - deterrents in their own right - will reduce the probable

damage that would result from biological weapons use in a particular operation.

The most sinister offensive biological warfare scenario employs surprise, immediate proximity, and rapidly lethal, persistent agents in overwhelming quantities. Under these circumstances, real-time sensing, donning of physical protection, and conventional non-medical countermeasures are only marginally effective. An effective operational defense ideally requires instantly available or emplaced countermeasures that can defeat biological threats as they enter the body and before they reach and attack target cells and tissues.

The focus of the Unconventional Pathogen Countermeasures Program is the development of revolutionary, broad spectrum, medical countermeasures against significantly pathogenic micro-organisms and/or their pathogenic products. These countermeasures will be versatile enough to eliminate biological threats, whether from natural sources or modified through bio-engineering or other manipulation. They will also have the potential to protect both within the body and at the most common portals of entry (e.g., inhalation, ingestion, trans-cutaneous). Strategies include but are not limited to:

1. Defeat of a pathogen's ability to a) enter the body b) traverse the bloodstream or lymphatics and c) enter target tissues.
2. Identification of novel pathogen vulnerabilities based upon fundamental, critical molecular mechanisms of survival or pathogenesis (e.g., Type III secretion, cellular energetics, virulence modulation).
3. Construction of unique, robust vehicles for the delivery of countermeasures into or within the body.
4. Modulation of the advantageous and/or deleterious aspects of the immune response to significantly pathogenic micro-organisms and/or their pathogenic products in the body.

Biological Warfare Defense

This program is developing advanced point detectors for biological warfare agents and extending the combat informatics program to biological warfare defense. Currently, planned DoD detection schemes are quite large, require a long time for identification (hours), and require a man in the loop. The DARPA program is developing detectors with minimal to no false alarms and small size (on an electronic chip) that can be operated unattended. The BW Defense informatics thrust is developing the capability to deliver information to the field medic about BW treatment protocols and to provide BW casualty information to the medical and field commands.

Unconventional Pathogen Countermeasures

Program Manager:

CDR Shaun Jones, M.D., USN

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Current Solicitations:

BAA 97-23 Pathogen Countermeasures

Advanced Diagnostics

Program Manager:

Dr. Stephen Morse

Countering the BW threat will require Advanced Diagnostics. Under real-world circumstances, an attack with a biological agent may occur without warning, and the first indication that an attack has occurred may be the appearance of sick personnel. Immediate diagnosis, and the ability to identify those who have been exposed but have not yet developed signs or symptoms, will be essential for effective response. Disease caused by different biological agents will require different courses of action, but may often begin with the same vague initial symptoms. The same symptoms may also be caused by a variety of natural infections, which will need to be differentiated. In addition, the capability to identify hitherto unknown natural infections and bio-engineered agents will be essential. Time constraints require the ability to test appropriate samples with minimal or no preparation. Because military operations can occur in virtually any locale, diagnostics should be able to function under extreme environmental conditions. By contrast, current methods for pathogen identification often require specialized skills and reagents and may take hours or days to complete. This could lead to potentially disastrous delays in responding appropriately to the threat or to the possibility of inappropriate action based on inadequate information.

The objective of the Advanced Diagnostics Program is to provide the capability to detect in the body, in real time and in the absence of recognizable signs and symptoms and when pathogen numbers are still low, the presence of infection by any pathogen. Specific areas of interest include but are not limited to:

1. Multi-agent diagnostics capable of simultaneously identifying a broad range of pathogens (infectious agents and/or their products) in clinical samples or in the body.

2. Strategies for identifying both known and presently unknown or bio-engineered pathogens (e.g., diagnostic approaches based upon fundamental, critical mechanisms of pathogenesis, targets shared by classes of pathogens, or early host responses to infection).

3. Capabilities for continuous monitoring or immediate recognition of infection in the body.

4. Wearable diagnostics for noninvasive broad-spectrum detection of infection in the body.

Current Solicitations:

BAA 97-24 Advanced Diagnostics for Pathogens

Advanced Biological and Medical Technology

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Combat Casualty Care

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A principle technology focus of the Combat Casualty Care effort is in the area of advanced far-forward non-invasive diagnostics. This includes the development of a personnel status monitor for continuous measurement of individual physiologic vital signs, portable blood chemistry units, portable body imaging devices, and exploratory work in advanced telemedicine and telesurgery. Additional emphasis is placed on the development of technologies, more immediate medical and surgical intervention, advanced simulation to improve the training of battlefield health care providers and to ensure skill currency.

Biological Warfare Defense

This program is developing advanced point detectors for biological warfare agents and extending the combat informatics program to biological warfare defense. Currently, planned DoD detection schemes are quite large, require a long time for identification (hours), and require a man in the loop. The DARPA program is developing detectors with minimal to no false alarms and small size (on an electronic chip) that can be operated unattended. The BW Defense informatics thrust is developing the capability to deliver information to the field medic about BW treatment protocols and to provide BW casualty information to the medical and field commands. The Unconventional Pathogen Countermeasures program is a new effort to develop medical and non-medical countermeasures to prevent and treat infections of the warfighter. The program seeks to apply the latest advances in biotechnology to augmentation of the human immune response to pathogens. Another new effort is the Advanced Diagnostics Program. The objective of the Advanced Diagnostics Program is to provide the capability to detect in the body, in real time and in the absence of recognizable signs and symptoms and when pathogen numbers are still low, the presence of infection by any pathogen.

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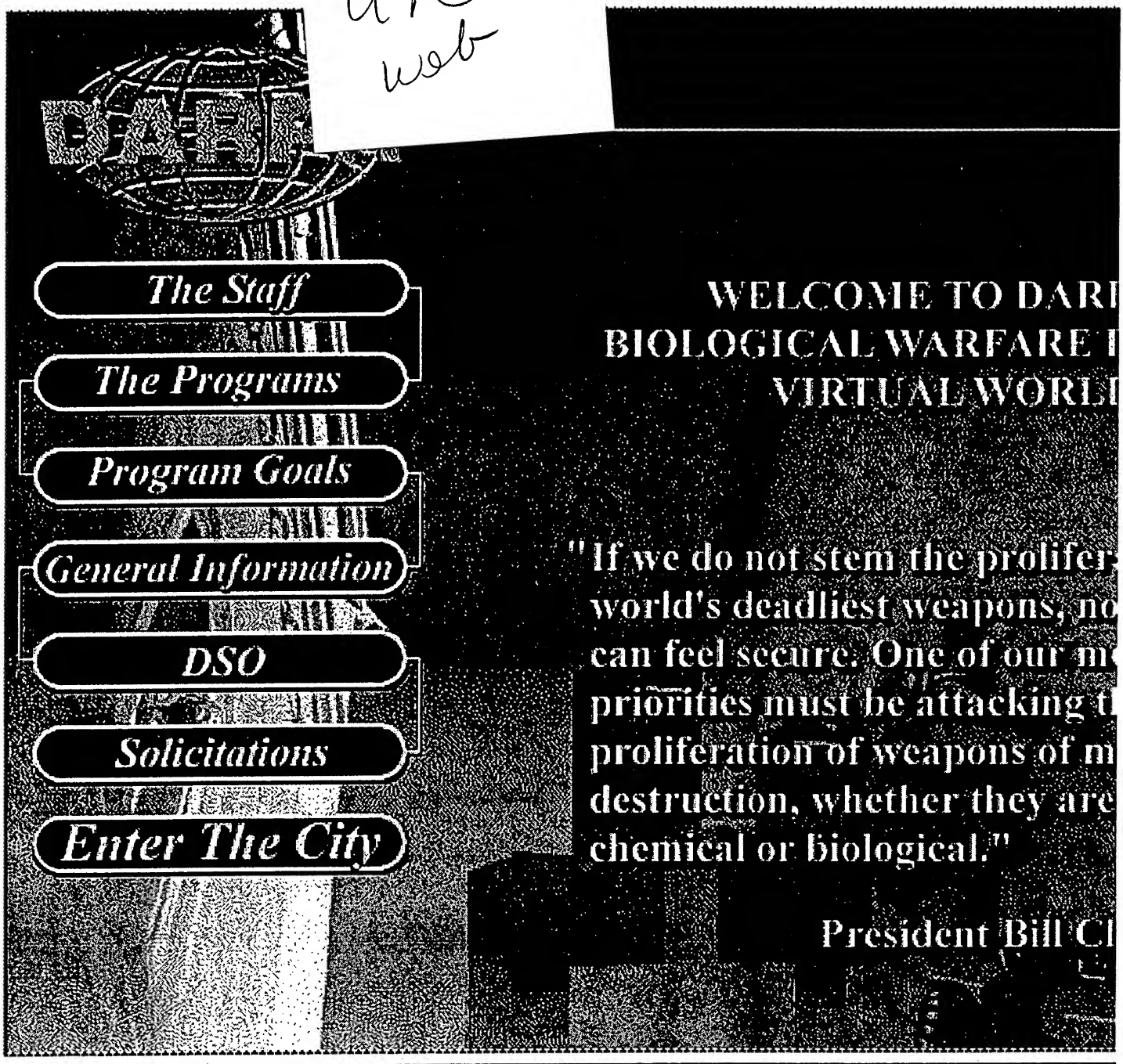
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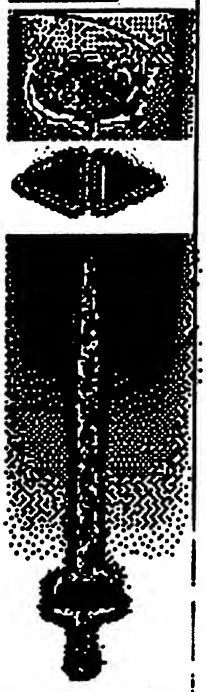
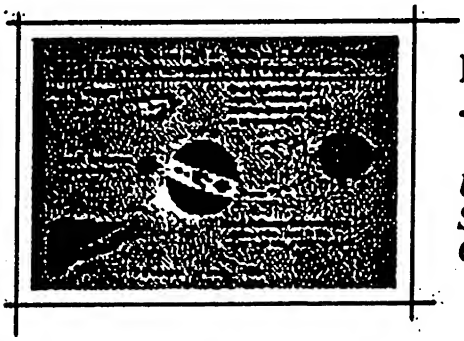
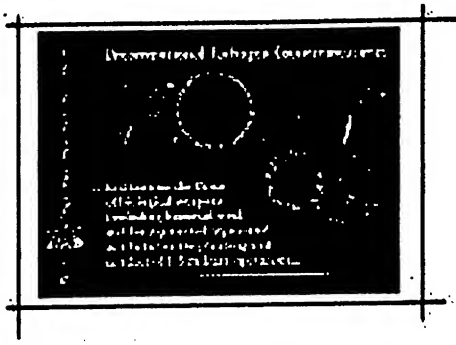




Red Blood Cell Pathogen Defense - Decoy

University of Virginia
School of Medicine
Charlottesville, VA

Research at the University of Virginia (UVA) is focused on the development of a new and general therapeutic approach for the safe and rapid clearance of pathogens from the circulation. UVA has prepared cross-linked, bispecific monoclonal antibody complexes (heteropolymers, HP) which facilitate quantitative and rapid binding of model target pathogens to the erythrocyte complement receptor. Once bound to the erythrocyte, the model pathogens are rapidly cleared from the circulation and phagocytosed and destroyed in the liver. UVA is investigating the use of HP for passive immunization and/or as a therapy for the acute treatment of infections associated with pathogens in the bloodstream. Their published work to date has demonstrated proof of principle for several model pathogens. UVA's present efforts are now directed toward a number of additional pathogens of potential significance as BW agents.



Red Blood Cell Pathogen Defense - Destruction

Mark Bitensky
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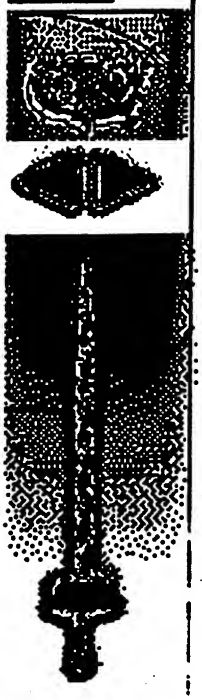
Boston, MA

The investigators at Boston University (BU) are exploring the use of the red blood cell as a platform to mount defenses against a variety of pathogens including bacteria, viruses, toxins and chemical agents.

In designing generic defenses against pathogens, certain characteristics are desirable:
CAPACITY: A technology that can serially and catalytically process and destroy pathogens offers the advantages of inexhaustible capacity.
SPEED: A technology that exhibits great processing speed also provides significant defense advantages in many scenarios.
LOCATION: A technology is most effective when situated so that pathogens must encounter the defense prior to reaching target cells or tissues.
FLEXIBILITY: A technology that can provide a multi-potential configuration which can be established as a generic in situ platform and can be rapidly adapted to different threats.

In considering candidate strategies that address the above requirements, BU was drawn to the concept of an intravascular location, with an enzymatic or multi-enzymatic capability (for inactivating pathogens) mounted on the erythrocyte surface. This approach provides both speed and capacity. A generic spectrum of attachment strategies provide flexibility by choosing common initial strategies for linkage to the red cell platform. These initial linkage configurations can be further specialized to the needs of a particular pathogen sub-class. Enzymatic capabilities are enhanced by utilizing synergistic components and focussed within micro-ensembles. These components will then be further optimized, using the tools of molecular biology, in order to provide sustained intravascular defenses against a spectrum of pathogens.



Sequential Auto Vaccination by Stem Cells

Daniel R. Marshak
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http://www.biospace.com/exhib_script/exhibitors/OsirisThe
Baltimore, MD

Project 1 targets the sequential release of vaccines utilizing human mesenchymal stem cells (hMSCs) as a biological platform to deliver the antigens. The project is directed toward demonstrating that hMSCs can be used to provide immunizations against several biological agents without the adverse toxic effects of multiple vaccinations administered simultaneously. Products derived from this research would provide a direct benefit to the military and civilian medical communities through new approaches to multi-vaccine activation and delivery.

Project 2 concerns the use of human mesenchymal stem cells (hMSCs) to create a defense system that can detect and detoxify an organic agent in the body. In this two-component cell system, one population of cells would be genetically engineered to produce a unique biological product in response to exposure by a specific toxic agent. A second population of cells would then respond to the signal and release a genetically programmed detoxifying agent.

DARPA Explores Some Promising Avenues

By Nancy Tomich

ARLINGTON, VA.—The Defense Advanced Research Project Agency's envelope-pushing attempt to halt hostile pathogens within the body already has targeted some promising routes for exploration.

DARPA's "unconventional pathogen countermeasures" program is in the process of awarding 12 contracts aimed at the admittedly "revolutionary" goal of priming the body to incapacitate lethal or debilitating biologic agents released by an enemy on the battlefield—or elsewhere.

"There is a tremendous mismatch between our capabilities for dealing with the threat and the potential that exists from various rogue states and terrorist organizations," observed Stephen S. Morse, PhD, manager of DARPA's Biological Warfare Defense Program. "I think it's becoming increasingly recognized how important that threat is."

While some in the scientific community scoff at the medical-countermeasures program as "pie in the sky," making such pies is precisely DARPA's mission, advises Cdr. Shaun B. Jones, MC, USN, program manager in DARPA's Defense Sciences Office.

DARPA announced the $30 million Biological Warfare Defense Program as part of two "broad agency announcements" (BAAs) released last June [the other one dealt with detection and identification technologies for biological threats and offered $4 million in funding].

More than 200 responses were received to the biological countermeasures announcement, related Dr. Morse, and the 12 projects selected were identified by an academic advisory panel as the ones with greatest potential. DARPA already had three such projects in progress, making a total of 15 in the biological countermeasures area.

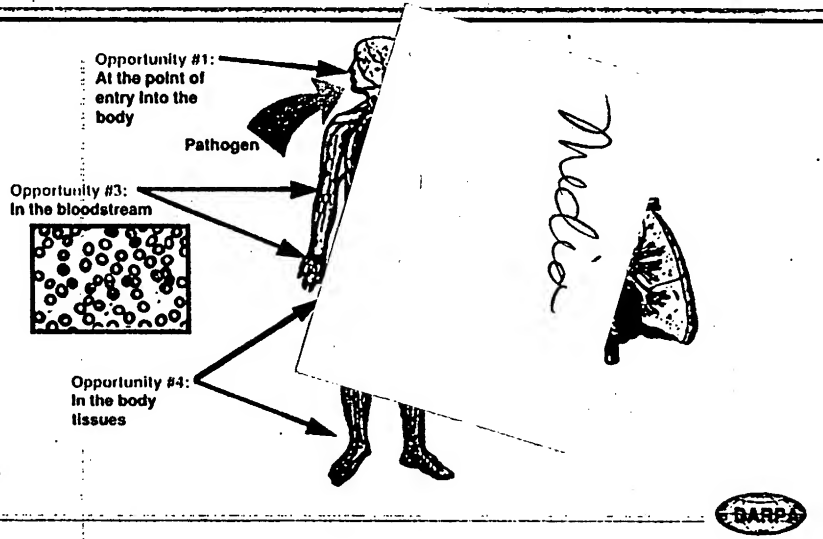
The advisory panel for the countermeasures program is chaired by Dr. Joshua Lederberg, with whom Dr. Morse previously worked at Rockefeller University, dealing extensively with the issue of emerging infections. Dr. Morse is a cofounder of ProMED, the Internet-based "Program for Monitoring Emerging Diseases."

An industrial advisory panel also is being created for the countermeasures program to help evaluate the research being funded and bring it to fruition.

DARPA's countermeasures program

(Continued on page 26)

Defense Against Pathogen Attack: a Multi-Level Approach



DARPA Explores Some Promising Avenues

(Continued from page 1)

deals only with biological agents, emphasized Dr. Jones, and only with defense against them: "There are no offensive programs in the U.S., anywhere."

Revolutionary Technologies

DARPA's role, related Dr. Jones, is to provide "complementary technologies" to other efforts within the Defense Department, which spends about a half to three-quarters of a billion dollars a year on chemical and biological warfare defense programs. "This really isn't an attempt to come in and take over projects or make technologies better that are in existing programs. We're really trying to create technologies that are revolutionary in their capability, which is DARPA's legacy—we've created revolutions in so many other disciplines, and we seek to do that here." (DARPA, for example, developed the Internet.)

"We realize we may fail," Dr. Jones added. "But that which is successful will provide a revolutionary advance in capability in defense *and* will be naturally complementary to ongoing efforts."

"While no defense may stop a determined adversary from introducing biological weapons into combat, a sufficiently robust array of pathogen defenses and countermeasures—deterrents in their own right—will reduce the probable damage that would result from the use of biological warfare in a particular operation," states the BAA for the countermeasures program. "It is DARPA's intent to emphasize development of those pathogen countermeasures that will have the greatest impact on the protection of uniformed warfighters and the defense personnel who support them during military operations."

The BAA requested proposals that are "strongly grounded in scientific and medical principles, yet revolutionary and forward thinking in scope and promise."

Biological weapons represent the "poor man's nuclear bomb," said Dr. Jones, because the scientific wherewithal for making them is widely dispersed. "You can buy the equipment necessary to create biological warfare agents in kilogram quantities, and all that you need to do so is a university-level education, a desktop, and very little money—maybe $50,000. You can start from very few pathogens, and within a short time-period have an enormous lethal capability."

One equation bandied about in BW circles as a rule of thumb: 10 kg of a biological agent "appropriately used" has the lethality of a 10-kiloton nuclear weapon.

Determining compliance with treaties banning the use of biological agents is problematic, Dr. Jones noted, because one bacterium today can grow into an enormous quantity within a week.

Four Tiers

The "overarch-ing strategy" underlying the countermeasures program is to focus on "the most sinister scenario," Dr. Jones related, "because everybody else was working on the easier problems."

What is that scenario? "That we are surprised," he said. "We have no notice. Our sensors have not given us advanced warning. We have no chance to put on protective gear or defend ourselves. We *have been* contaminated with biological weapons, and we have limited time to respond and limited ability to respond."

Dr. Stephen Morse

The countermeasures program—while dynamic and constantly evolving—has identified several "tiers" for defense against such a scenario. The first tier is the "portals of entry" into the body—inhalation, ingestion, through the skin. The second tier is at the areas before the pathogen enters the bloodstream, such as the lungs and the intestinal tract; the third is the bloodstream; and the fourth, the body tissues.

Within each tier, multiple defenses have been envisioned. "We really have an onion-skin kind of defense, and within each layer we have multiple defenses," Dr. Jones explained. "This is really woven, and redundant and, we hope, powerful."

Dr. Jones said he has been "personally ridiculed out of many conference rooms" over DARPA's ambitious, "blue sky" approach to in-body defenses. But, he added, there may be crow on the menu for those who have laughed, because already a few of the projects look extremely promising.

One project he points to in example involves the concept of using red blood cells as a defensive platform: "We would decorate the red blood cells with biological black boxes, and they would remove pathogens that got into the blood stream and deliver them to the regions in the body for pathogen destruction, the reticuloendothelial system."

Now, Dr. Jones said, with what might be likened to parental pride, this admittedly "pie in the sky" approach looks feasible. Ronald Taylor, a physical chemist at the University of Virginia, was able in monkeys to take red blood cells, label them with "biological black boxes"—which really are double-ended constructs called heteropolymers—and have one end of those "boxes" bind to the pathogen and the other end to the cell.

"He could inject these double-ended molecules into the bloodstream of the monkeys, and they would bind 99 per cent to the red blood cells, and not to other places," Dr. Jones explained, "The red blood cells, once decorated, circulated in a normal fashion, they carried oxygen in a normal fashion. We're not sure why, but they don't activate the clotting cascades, they don't cause a powerful immunogenic reaction."

Dr. Shaun Jones

It's entirely possible, he said, that soldiers—or civilians—under biological attack could simply receive an infusion of the "black boxes." Initial data indicate that when a virus-simulant is put into direct contact with the "black boxes" in the bloodstream, there is a million-fold reduction in its numbers in less than an hour. Further, the ability to produce this level of reduction in pathogens persists for at least five days.

Dr. Jones notes that Dr. Taylor's so-called "pie in the sky" project was turned down four years in a row in the peer review process at the National Institutes of Health. "This is the pie-in-the-sky on which we 'frivolously' spent our money—and we now have powerful results!" He grins.

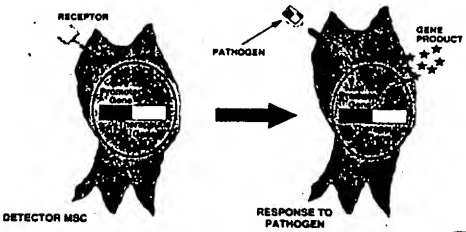
Redundancy Sought

While a defense against hostile pathogens such as the "black-box" construct still would require warning that an attack was imminent, so that an injection could be made, it is but one of numerous strategies being pursued, Dr. Jones said. "We have 15 different programs, and what we're trying to provide is redundancy and multiple defenses. One of the things that's quite scary is the number of pathogens that we face."

In fact, Dr. Jones said, there are "two prongs" to the unconventional pathogen countermeasures program: to design revolutionary defenses against specific pathogens, and to put these defenses together

(Continued on page 27)

Modified Mesenchymal Stem Cells Detect Pathogens and Release Products



CAPSULES

• OFFICIALS IN the Veterans Health Administration are trying to cope with an uncertain fiscal future, while VA secretary Jesse Brown again reassures members of Congress that the administration's fiscal 1998 budget plan will not reduce funding. Page 1.

• A PROJECTED budget deficit for defense medical programs draws weary sighs on Capitol Hill, where the shortfall likely will be rectified. Page 1.

• SOME PROMISING avenues are being explored by DARPA in its effort to halt pathogens within the body. Page 1.

• HOME test kits add a new dimensions to the epidemiology of HIV infection and how counseling is provided. Special report. Page 2.

• LAND MINES and their terrible trauma draw joint U.S.-Russian attention. Page 3.

TELEMEDICINE in DoD increasingly is taking the store-and-forward approach. Page 3.

• RESEARCHERS HIGHLIGHT advances made in substance abuse with VA support. Page 3.

• BEFORE HE left the Pentagon assistant secretary of defense for health affairs Dr. Stephen C. Joseph examined the issues facing military medicine. Interview. Page 18.

Departments

NCID Infection Watch

Dr. James M. Hughes, director of the National Center for Infectious Diseases at the Centers for Disease Control and Prevention, regularly reports on issues relating to new and re-emerging infections.

Implementing CDC's Emerging Infections Plan

The World Health Organization (WHO) has estimated that in 1995 approximately 17 million of the 52 million deaths, or about one-third of the deaths that occurred worldwide, were caused by infectious diseases. The leading killers are acute lower respiratory infection, diarrheal disease, tuberculosis, malaria, hepatitis B, measles, and AIDS. We often lose sight of the fact that infectious diseases are also a very important cause of mortality in the United States; when infectious diseases are aggregated, they represent the third leading cause of death in this country behind heart disease and cancer.

The Institute of Medicine report, *Emerging Infection, Microbial Threats to Health in the United States*, published in 1992, contains 15 recommendations. Over half of the recommendations were targeted at CDC and most of them were directed at the National Center for Infectious Diseases. We moved forward with input from our many constituents and partners to develop the CDC Emerging Infections Plan.

This plan, published in 1994, was being developed during the time that we encountered the E. coli 0157:H7 outbreak associated with a fast food restaurant chain in the western U.S. The plan was also shaped by the experience of the waterborne cryptosporidiosis outbreak in Milwaukee, which occurred in the spring of 1993, and the episode of severe, highly fatal acute pulmonary disease initially detected in the Southwestern United States and rapidly identified as hantavirus pulmonary syndrome.

The CDC plan contains four major goals. The first goal stresses the need to strengthen surveillance and response capacity. The second identifies applied research priorities, the third focuses on the need to strengthen prevention and control programs at the local, state and national level, and the fourth focuses on priorities for repair of the public health infectious disease infrastructure that has deteriorated during the past 25 years.

We estimate that full implementation of the CDC plan will cost approximately $125 million per year. Through fiscal year 1997, Congress has appropriated $44 million to CDC to address these needs.

We have established seven Emerging Infections Programs. We encourage state health departments to work with partners in their geographic area; in some cases this has involved local health departments, state APIC chapters, schools of public health, schools of medicine,—particularly the academic infectious diseases divisions—managed care organizations, and in at least one case, the state medical examiner's office. These programs focus on three core projects: invasive bacterial diseases, unexplained deaths in individuals between the ages of 1 and 49 years of age, and foodborne disease. The foodborne disease project is the result of an interagency agreement between CDC, the FDA and USDA.

In addition, each of the emerging infection programs has the latitude to focus on two to three additional local infectious disease priorities. Having these emerging infectious programs in place has recently allowed us to rapidly assess both the extent of Cyclospora in the United States and the possibility that cases of new variant Creutzfeldt—Jakob disease (CJD) were occurring in this country. No cases of this new variant CJD have been identified.

We have also been able to provide financial assistance to 13 other states and two large cities (Los Angeles and New York) to address critical gaps in their epidemiology and laboratory surveillance and response capacity. Some have elected to focus on improving surveillance, providing training and technical assistance for local health departments, developing electronic disease registries, and forming partnerships with managed care organizations.

We have entered into cooperative agreements with three organizations to establish sentinel emerging infectious networks. One is based in emergency departments in academic medical centers; a second, in collaboration with the Infectious Diseases Society of America, focuses on problems seen by infectious disease physicians; and a third focuses on traveler's health clinics in collaboration with the International Society of Travel Medicine.

The second area of emphasis is research. We have elected to focus initially on antimicrobial resistance and emerging tickborne diseases, specifically ehrlichiosis and babesiosis. This research is complementary to the type of efforts identified by the National Institute of Allergy and Infectious Diseases in its research agenda for emerging infectious diseases.

The third area, prevention and control, requires effective, timely communication of information on disease trends and research results. The CDC Emerging Infectious Diseases journal is available at no cost in hard copy and is also accessible over the Internet through the CDC home page (http://www.cdc.gov).

In terms of infrastructure, we are increasing our role in public health laboratory training. We have established an Emerging Infectious Diseases Laboratory Fellowship Program. We have had two classes of laboratory fellows begin with assignments in CDC laboratories or in state public health laboratories.

Since infectious diseases are important, evolving, complex public health problems, their prevention and control will increasingly require application of sophisticated epidemiologic, molecular biologic, behavioral, and statistical approaches and technologies. It is hard to predict exactly what challenges we will face in the future, but we can anticipate increased problems from antimicrobial resistance, the risk of the next pandemic influenza outbreak, and concerns about urban yellow fever returning to South America. Recent experience tells us that we are going to continue to see regional, nationwide and international foodborne diseases outbreaks. We will very likely learn that more chronic diseases have an infectious cause. Finally, we have to be prepared to confront unexpected challenges from the changing microbial world.

CDC is organizing a conference on emerging infections that will be held in Atlanta on March 8-12, 1998. The conference will focus on disease threats and trends and review progress in implementation of national and global strategies to address these challenges.

— James M. Hughes, M.D.

Too Radical for NIH? Try DARPA

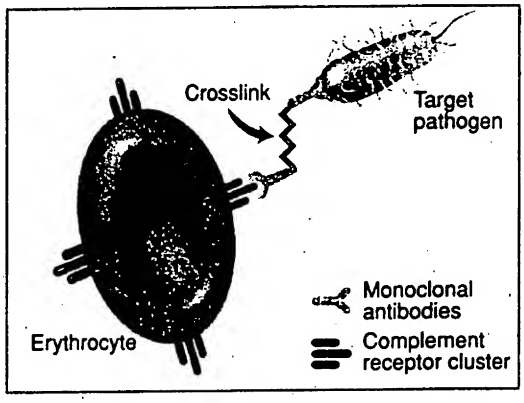
Alarmed by evidence that terrorists may exploit biological weapons, the Internet's sponsor is moving into a brand-new field with some serious money

You have a radically new idea for fighting pathogens that your colleagues are dubious about—a scheme, say, to program blood cells to remove viruses from the bloodstream in minutes. Where would you go for funding? To the National Institutes of Health (NIH), the big bank of biomedical research? Perhaps. But NIH would ask a committee of peers to evaluate your idea, and peers can be brutal about radical concepts. For the same reason, you would not expect much enthusiasm from private charities or from public health agencies like the Centers for Disease Control and Prevention. But there is one federal outfit that says it loves revolutionary ideas, and it has just begun spending millions of dollars on pathogen research: the Pentagon's wunderkind, the Defense Advanced Research Projects Agency (DARPA)—best known as the originator of the Internet.

For 3 decades, DARPA has been bankrolling far-out engineering and electronics projects, and about 2 years ago, its leaders got interested in biology. Now, they are talking about spending serious money on basic and applied science projects to protect the military—and maybe civilians—from biohazards. According to Jane Alexander, deputy director of DARPA's basic sciences division and an electronics expert, the agency aims to fund about $40 million to $50 million worth of biodefense research this year. By 1999, DARPA may be spending $100 million, and after that, she says, "we may aim at a $200-million-a-year effort."

That would be a good chunk of DARPA's budget, now $2 billion a year. The commitment reflects the concern of DARPA's new director, Larry Lynn, about the risk of biological attack by "rogue governments" or terrorist groups (see sidebar). Lynn, who majored in physics as an undergraduate and has spent his career managing defense projects for the military and industry, was appointed by President Clinton to take over DARPA in 1995. He set out to reorganize the place quickly, and in 1996, DARPA emerged a smaller, more focused agency, with newly defined objectives. And there was something entirely new on the list: basic biology, a field DARPA had never funded before. Lynn told Congress last year that "biological warfare defense" is fourth of the top nine military problems DARPA wants to tackle and that "biological systems" are among the top nine technologies the agency has targeted for development.

Congress approved, making biodefense research a line item in DARPA's budget last year, and the agency moved eagerly to take up the assignment. Outsiders have also been swept up: "I feel the enthusiasm," says Stanford University biologist Stanley Falkow, current president of the American Society of Microbiology, who has served as one of DARPA's advisers from academia. "I think we'd be mistaken if we didn't address" the threat of assault by biological weapons, he says, both as a military issue and a public health risk. But Falkow, who says he is doing "a little work" himself with DARPA support, is hedging his bets on the likelihood of success. The ideas DARPA is funding, he says, "sound wonderful," but no one knows how well they're going to work.



Blood sweeper. DARPA is investing heavily in this idea for removing pathogens from the bloodstream.

Outside researchers add that agency wizards—accustomed to quick-turnaround engineering projects—may be unrealistic about what can be done in biology on a short schedule. DARPA is "quite serious for the moment," says one scientific adviser, but he worries about what will happen if the excitement passes. In engineering and computers, says Michael Donnenberg—a microbiologist at the University of Maryland, Baltimore, who advises DARPA—the agency tends to support an experiment at one lab for a couple of years, then move the experiment to another place. In contrast, says Donnenberg, NIH-funded researchers "are used to 5-year cycles ... and then getting refunded." DARPA's hands-on management style may also ruffle biologists, he says.

DARPA officials acknowledge that they are taking a big gamble. But one staffer says, with a touch of hubris, that this is exactly why DARPA is betting on "only the best" advisers and ideas.

Star Wars of biology

Lynn set DARPA on this new course, he says, because biological threats are becoming "more acceptable" as weapons of terror. "Probably they are next to nuclear weapons in the magnitude" of damage they might cause, while being "much easier to build and dispense, with relatively rudimentary training," he adds. While the Department of Defense is already spending "a fair amount of money" to cope with "near-term" issues—developing better protective gear and refining vaccines—this work tends to be agent-specific and limited to immediate worries, Lynn says. DARPA likes bigger challenges.

"We are concerned with a much broader range of agents than you would think of today," says Lynn. DARPA is especially concerned about genetic engineering, and it has set an extremely ambitious goal—reminiscent of the Star Wars antimissile program. Lynn says the aim quite simply is to "eliminate biological weapons as a serious threat to military activities." Along the way, DARPA may inspire researchers to develop products useful to the civilian economy, like new antibiotics.

DARPA prides itself on moving fast, and it has already blitzed into pathogen studies and immune-system research. It has recruited a blue-ribbon panel of academic advisers that includes eight members of the National Academy of Sciences and is chaired by the president emeritus of Rockefeller University, Joshua Lederberg. Lynn himself has been visiting biotech companies—"a wild lot," he says, adding that "when you mix them with a funding organization that's willing to play wild, a lot of excitement gets generated." DARPA last year issued two invitations to scientists to submit proposals for research contracts totaling $50 million. It received more than 250 responses, and is now signing contracts with the winners, which include both biotech ventures and nonprofits.

Although a full list of awardees wasn't available at press time, DARPA staffers mentioned some of the early winners and outlined for *Science* a few of the concepts they are exploring. One award, worth "millions," according to a consultant, has been

signed with Molecular Geodesics Inc. of Cambridge, Massachusetts. The aim: to design synthetic "bioskins," filters, and other protective gear based on principles of cellular structure elucidated by Donald Ingber of Harvard Medical School. Another contract will go to Isis Pharmaceuticals Inc. of Carlsbad, California, to create "novel, broad-spectrum antimicrobial agents." And a third will go to The Scripps Research Institute in La Jolla, California, to create a library of "invasive intracellular antibodies" for use in the development of exotic new therapeutic agents.

As an example of the kind of high-risk, potentially high-payoff, basic science experiment the agency wants to fund, Alexander and Commander Shaun Jones, program director for unconventional pathogen countermeasures, described a project involving blood research DARPA began funding last year. Jones says he was "laughed out of conference rooms" when he first talked to biologists about this project—an idea developed by physical chemist Ronald Taylor of the University of Virginia, Charlottesville. But now, it's being taken more seriously.

Taylor says he had established by 1991 that previous studies had overlooked the importance of a pathway in primates for clearing foreign bodies from the bloodstream. He concluded that a receptor called CR1 on the surface of red blood cells plays a key role in removing material tagged as alien by the immune-system proteins known as complement. Once bound to the receptor, the material is quickly flushed out of the body by the liver. (A report on his initial work was published in 1991 in the *Proceedings of the National Academy of Sciences*.) Taylor looked for a way to improve upon CR1's ability to clean up the blood. Borrowing an idea developed in the 1980s at Dartmouth, he created a "bispecific" polymer that hooked at one end to CR1 and, at the other, to almost any protein one might want to target.

The idea didn't fare well in peer review: After several rejections, Taylor finally received support from NIH in late 1995 to carry out a narrowed-down experiment focused on proteins in autoimmune disorders. In mid-1996, however, DARPA picked up Taylor's big idea and now regards it as one of its great finds. With DARPA's funding, Taylor and his colleagues have already shown in rhesus and cynomolgus monkeys that the polymer-CR1 system can be used to move huge quantities of a model virus (ϕX174) in 90 minutes from the blood to the liver. Neither the blood nor liver appears to be adversely affected.

Jones says he's "very excited" about these results and about the potential payoffs of a more recent, unpublished study. Jones says this work suggests it may be possible to "decorate red blood cells in a variety of ways" that will enable the cells—the "platform," in DARPA parlance—to process 10^{13} or more pathogens per minute.

These blood-based studies fit into one major category of projects DARPA is funding, called pathogen countermeasures. The program also includes an even more visionary scheme that would engineer mesenchymal stem cells—the source of muscle, fat, bone, and cartilage—that can sense and respond to biological threats. According to Jones, the program director, cells bearing a "cassette" of transplanted genes would populate the recipient's tissues and, in theory, recognize certain pathogens and turn on genes to produce an appropriate response.

In a variation on this idea, Jones says, the program is interested in developing cells that would "autovaccinate" the body against biological threats, avoiding the need for repeated injections and all the problems they create. It sounds far-out, but DARPA has already paid an animation company in Iowa to create a three-dimensional (3D) movie illustrating how such exotic battles might be fought within the human body. Members of the academic advisory board said they donned special 3D glasses to watch the cartoon at a meeting sponsored by DARPA last December in Santa Fe, New Mexico.

On a less fantastic level, DARPA is studying a concept from basic biology—the idea that pathogens may share some common, fundamental vulnerabilities that remain undiscovered. Both Falkow and microbiologist John

Bracing for a Biological Nightmare

Leaders of the Defense Advanced Research Projects Agency's (DARPA's) new biology program say that several recent biological-weapons threats goaded them into action to develop countermeasures. Close to home, a man associated with survivalist groups was arrested in 1995 for trying to smuggle 130 grams of ricin—a plant toxin that can cause death within minutes of contact—into the United States from Canada. And in separate incidents, others were arrested or convicted in 1995 on charges of illicit use of ricin or bubonic plague. While police work avoided tragedy in these cases, DARPA officials warn that next time, it may not.

The most shocking case in point occurred on 20 March 1995, when the Aum Shinrikyo religious group attacked passengers on Tokyo's subway trains with nerve gas, killing 12. This cult—more than 60,000 strong by one estimate—used a global network of offices and a technically skilled membership to buy hardware and manufacture weapons in secret. After the Tokyo attack, investigators discovered that Aum members had built crude biological weapons, including a bomb containing anthrax, whose bacterial spores enter the lungs and—unless treated quickly—lead to inevitable death. They may have set off one anthrax device in Tokyo, but it didn't work. (One U.S. pathogen expert warns: "I could make one that works, but don't tell [the Aum cult]—they might kidnap me.") Other evidence suggests that Aum members were trying to collect the deadly Ebola virus and manufacture botulinum toxin. Police also found that Aum members in New York and Japan had purchased sophisticated molecular-design software and bacterial growth media, an indication, according to the U.S. Senate Permanent Subcommittee on Investigations, that the cult was trying to engineer deadly new bacteria.

AP/WIDE WORLD PHOTOS

Wake-up call. Nerve gas attack in Tokyo got DARPA's attention.

Another wake-up call was the extensive bioweapons stockpile built in the late 1980s by Iraq's military under Saddam Hussein. The United Nations Special Commission (UNSCOM) on Iraq, chaired by Swedish diplomat Rolf Ekeus, reported in October 1995 that Iraqi officials admitted to running a large biological weapons program. Included in the acknowledged inventory, according to UNSCOM, were 19,000 liters of botulinum toxin (10,000 liters of which had been put in weapons); 8500 liters of anthrax (6500 liters in weapons); 2200 liters of aflatoxin, which causes liver cancer (1580 liters in weapons); and smaller quantities of hemorrhagic conjunctivitis virus, mycotoxins, and ricin. Some of these agents—including botulinum, anthrax, and aflatoxin—were loaded into 25 SCUD missile warheads. —E.M.

Mekalanos of Harvard University have been doing research on the genes that make pathogens virulent, and DARPA has been consulting both of them on how to exploit their work. Mekalanos is enthusiastic, but even if his work does find a new Achilles' heel of cholera, for example, he wonders how far it can be developed without support from industry: "You're going to have to bring big pharma into the equation ... because it still costs $200 million to develop one antibiotic." Jones agrees, adding that he is working hard to create an advisory group "without peer" drawn from industry and hopes that companies will be joining DARPA's effort.

New focus. Larry Lynn has made biology a priority.

In other project categories, DARPA is gearing up to support the development of quick sensors to detect and identify biological threats, medical and body-shielding techniques to counter an attack, and better computer systems for managing the response to an attack. One biosensor concept, according to DARPA's Alexander, consists of a single neuron stabilized in a silicon-chip array that monitors the cell's response to possible nerve agents in the environment—a fast, reliable, and portable system for detecting neurotoxins. Affymetrix Inc. of Santa Clara, California, a company that specializes in chip-based genetic analysis, and biochemist George Whitesides of Harvard University have both contributed expertise to the effort, which DARPA calls a "canary on a chip." A related project, Alexander says, aims to use color-coded fluorescent sensors linked to a variety of specific antibodies to give a quick readout on the contents of an incoming cloud from a biological weapon.

Skeptic academics

Jones is optimistic about developing these ideas into real products. At the same time, he adds that "I understand there is skepticism" in the academic community, but suggests that it exists in part because "there has not been the equivalent of a DARPA in the biological life sciences" until now. People may not appreciate how much can be accomplished when money is applied in a focused effort.

But one of DARPA's academic advisers who asked not to be named says he was "not overwhelmed by the choice of projects" in the initial round: "More than one was chosen that wasn't favored by the advisory panel." DARPA is "looking for another Internet," he adds, and he worries that this ambition may cause it to overlook unglamorous projects that deserve backing. Another biologist-adviser, asking not to be named, was disappointed for the opposite reason: He thought initial applications were not ambitious enough. DARPA "has a lot of money, and they want you to be really imaginative." But "we got a lot of rather conventional, good-science proposals" that didn't seem likely to cause any revolution.

Some also wonder whether biologists—an independent lot—will submit to DARPA's aggressive, team-dominated supervision. Maryland's Donnenberg notes, for example, that DARPA staffers "totally manage the whole thing. ... If a proposal is good, they think nothing of saying, 'How about you drop three of your specific aims, add a fourth, and collaborate with this other person?' " He sums up the approach thus: "We'd love to give you the money, but only if you study this instead." And Richard Lerner, president of The Scripps Research Institute, another DARPA adviser, notes that the agency needs to keep in mind that "you never know what you want to discover until you discover it."

But these and other scientists who know about DARPA's new project are generally supportive. For example, John La Montagne, infectious-diseases chief of NIH's National Institute of Allergy and Infectious Diseases, says he views the biodefense initiative as "complementary" to, and "much more applied" than, NIAID's work. As for Lerner, he seems delighted that molecular biology may have a new sponsor, as the Pentagon shifts its research focus from nuclear Armageddon to what Lynn calls "our war with Mother Nature." "Wouldn't it be nice," Lerner muses, "if one of the peace dividends is this kind of research?"

–Eliot Marshall

FRANCE

Archaeologists Take to the Streets

PARIS—A dispute sparked when construction work threatened an archaeological site in the southern French city of Rodez has become a rallying cause for French archaeologists. Last month, many researchers staged a weeklong strike, and 250 archaeologists and their supporters occupied the culture ministry's archaeology offices in Paris. These protests culminated in a demonstration that brought more than 1000 people onto the streets of Paris last week. Their goal: to persuade the government to pass new laws to protect vulnerable historic sites.

They got a swift response. On 29 January, French culture minister Philippe Douste-Blazy—who a week earlier agreed to temporarily halt construction in Rodez to allow rescue work to go on—told the protesters he would open a "great national debate" on the future of French archaeology.

Researchers initially put down their tools in mid-January to protest the potential destruction of vestiges of medieval, Gallo-Roman, and Iron Age structures in Rodez. The action came when it was revealed that French Prime Minister Alain Juppé had written to a local official 2 months earlier giving a developer the green light to continue construction of an apartment building at the site. Juppé's intervention circumvented efforts by the culture ministry, which had been negotiating with the developer to allow researchers to perform a brief mission of "rescue archaeology," to carefully record remains before construction proceeded. But the negotiations had stalled because the developer balked at paying for the study, which is the custom in France and many other countries.

Because France has regulations to protect sensitive sites, Juppé's action was "completely against the law," claims archaeologist Vincent Krier, leader of one of France's four archaeologists' unions, all of which participated in the strike. Officials, stung by the strength of the reaction, quickly backtracked, and on 23 January, Douste-Blazy announced that construction work at Rodez would be halted. But the strikers were not mollified. They are now pressing for stronger laws to protect historic remains from the bulldozers, including a formal requirement that developers pay for rescue archaeology. "The [current] law doesn't specify who must pay," says Françoise Audouze, director of the Center for Archaeological Research, a network of labs associated with the CNRS public research agency. "The developers are starting to refuse" to provide the necessary funds, she adds.

Another key demand is for a change in the legal status of the Association for National Archaeological Excavations (AFAN), a 2000-member private organization that carries out most rescue archaeology in France under contracts with the government. The strikers are calling for AFAN to be turned into a public organization, a move that would formalize the government's responsibility for protecting threatened remains. As for the national debate promised by Douste-Blazy, its scope has yet to be defined. But researchers involved in the action of the past several weeks have their own ambitions: "We are going to change the landscape of archaeology in France," says Krier.

–Michael Balter

ROBERT MULLAN COOK-DEEGAN

Does NIH Need a DARPA?

The National Institutes of Health (NIH) recently celebrated the 50th anniversary of its Division of Research Grants with a symposium on peer review. NIH Director Harold Varmus introduced the theme of the day, likening competitive external peer review to democracy by invoking Churchill's quip: "the worst form of government except all the others that have been tried." The analogy captured a belief in peer review widely shared among those in the audience. There are a couple of problems with the analogy, however. First, it is wrong. Some agencies—notably the Defense Advanced Research Projects Agency (DARPA—or ARPA during some periods) and the armed services' R&D operations—have demonstrated that other methods work quite well, arguably as well as or better than those used at NIH. Second, comparing peer review to democracy implies a false dichotomy. A country cannot be at once a democracy and a dictatorship, but an agency can simultaneously use both peer review and other mechanisms to support research and development; indeed, several defense R&D agencies do just that.

Robert Mullan Cook-Deegan, a 1996 Green Center Fellow, is director of the National Cancer Policy Board of the Institute of Medicine and National Academy of Sciences.

Peer review has worked well, but that does not mean that it is the only way to fund research.

The chief alternatives to competitive peer review are formula funding methods, based on political, historical, or performance factors, and what might be called the DARPA model, in which staff experts decide how to distribute research funds. Formula funding would surely reduce transaction costs and could provide a stable flow of support to good researchers. The price of reducing transaction costs through formula funding, however, is loss of expert judgment about innovative promise. The desire to invest in such promise, as opposed to past performance alone, is a major reason agencies have come to rely on outside expert advice. But the DARPA approach is also a way to foster innovation.

DARPA's effectiveness depends on expert staff, clear mission, focused effort, and lean management. DARPA's main function is to quickly exploit new inventions, ideas, and concepts with potential military utility. Its 80 or so program managers distribute between $2 and 2.5 billion annually, supervised by a half dozen office directors, who in turn report to the DARPA director. Only one management layer exists between the DARPA director and the program managers. The entire DARPA staff is roughly comparable in size to that responsible for administering extramural funds for the National Center for Human Genome Research or one of the smaller NIH institutes that expend between $100 million and $200 million.

DARPA managers are hired for expertise, often from industry or academia, and typically serve for four years or less. Each handles $10 million to $50 million of research funding a year, of which at least 20 percent is intended for new investments. The money for new programs is a direct result of DARPA's ruthless willingness to kill programs that are not meeting expectations. Success results from a long-term strategy pursued by highly expert staff given great discretion to manage substantial funding commitments. Those staff are held accountable in quarterly reviews and detailed annual assessments by the DARPA director.

DARPA's effectiveness has clearly depended primarily on the quality of its staff. The first direc-

tor of DARPA's extraordinarily successful Information Processing Techniques Office (IPTO) in the 1960s, for example, was J. C. R. Licklider, who is belatedly achieving legendary status in the development of modern computing. Others who followed him at DARPA maintained that standard as major figures before, during, and after their tenures at DARPA. Imagine if NIH had worked the same way during the 1970s. It could have hired trailblazing researchers such as Herbert Boyer, Stanley Cohen, or future Nobelist Paul Berg to promote recombinant DNA research and innovators such as future Nobelists Frederick Sanger or Walter Gilbert to foster DNA sequencing technology.

In DARPA culture, managers are self-avowed scientific and technological fanatics. Their base skill is recognizing talent relevant to defense needs and providing funds for its expression. The institutional ethos is described as "80 decisionmakers linked by a travel office," emphasizing its highly interactive (at times intrusive) style. It is ironic that within one of the world's most notorious bureaucracies resides a tribe of rambunctious technological entrepreneurs.

Created by the Eisenhower administration in the wake of the Soviet launch of Sputnik, DARPA played a crucial early role in the development of computer time-sharing, interactive computing, space launch vehicles, satellite surveillance, lasers, stealth technology, and many other technological innovations. The 25-year history of IPTO is DARPA's best known program outside defense technologies. IPTO spawned the first departments of computer science, bolstered an academic base for large-scale integrated chip design at a time when that foundation was eroding perilously, and created the prototype for today's Internet. It is safe to say that many computing activities we take for granted in the 1990s, including e-mail, computer graphics, interactive computing, alternative chip architectures, and networking, can be traced to DARPA funding decisions made in the 1960s and 1970s.

The most serious threat to science under peer review is conservatism—the safe squeezing out the novel.

Biomedical success

The past three decades have also been a time of remarkable progress in biomedical research, and NIH has played a central role. NIH funding accounts for almost 30 percent of the world's biomedical research literature, compared to about 40 percent from other U.S. sources and about 30 percent from all foreign sources. The volume and excellence of U.S. biomedical research—as well as the innovative power of industries dependent on such research, such as pharmaceuticals, medical devices, and biotechnology—can largely be attributed to NIH and its system of peer review.

But is peer review the only way to achieve success in this field? In materials science, telecommunications, space, lasers, and microelectronics—other fields in which the United States is the world leader—the nation's advantages in R&D arguably derive as much from mission-oriented, agency-directed research and technology development as from peer-reviewed science. In many fields of engineering, mathematics, and physical sciences, the National Science Foundation's (NSF) base of peer-reviewed grants is complemented by other agencies' dynamic portfolio of mission-related science and technology, much of which is funded outside of peer review.

Many of these fields do seem more like engineering than pure science, and some assume that DARPA's funding procedures are suited to technology with definite aims, but not to science. Experience suggests otherwise. Packet switching for electronic communication, computer time-sharing, integrated large-scale chip design, and networking were as conceptually "basic" when DARPA was funding them as most molecular biological experiments are today. Nothing was there but a notion that computers could be made to do things they had never done before. When NSF and NIH both frowned on funding work in neural networks, Leon Cooper received funding thanks to the judgment of a program manager at the Office of Naval Research (ONR), which uses a mix of peer review and DARPA-like funding mechanisms. ONR also led the way toward single-atom chemistry,

"squeezed" states of light, and acoustics—all fields with a heavy dose of basic science.

Another reason to consider the DARPA approach is its lower transaction costs. Administrative review costs at NIH or NSF rise arithmetically with the number of applications. External costs, however, rise much faster as the percentage of proposals that are funded falls. If half of all proposals result in funding, which was the case at NIH several decades ago, one unfunded grant proposal is prepared for each one funded. When success rates fall to one in five or one in six, as they have in several areas, four or five proposals are wasted for every one funded. Preparing a grant proposal is a substantial effort, and the total external costs for all applicants may approach or even exceed the amount awarded to the successful one. Physicist Leo Szilard once noted that at some point in a competitive grant system, applying for grants would consume all a scientist's time, leaving none for research. With 15 to 20 percent success rates, a "Szilard point" where waste exceeds benefit is no longer a frivolous speculation but a real possibility. Whereas NIH extramural administrators spend most of their time crafting rules for competition and then selecting among applicants, DARPA staff spend most of their time keeping abreast of their field and camping in sparsely populated outposts along the technological and scientific frontier.

Many scientists and engineers fear that grant competition has pushed peer review well past its power to distinguish the truly outstanding from the merely excellent. The least painful solution to this problem, at least for the scientists and engineers seeking funds, is more money for grants so that more are funded, the success rate rises, the relative external costs fall, and reviewers need only separate the good from the excellent. To relieve the tension in the peer review system would require at least a doubling of federal research support in combination with a "birth control" policy to stem the growth of the applicant pool. Although NIH enjoys stalwart bipartisan support, a budget increase of this magnitude is unlikely, and even if budgets grow, the applicant pool may well grow faster, if history is any guide.

Even if a pilot test of a DARPA-like program is a success, it still should be considered as an alternative for a few select programs only.

Although important, budget constraints and administrative inefficiency are not the most compelling reasons to experiment with DARPA-like funding mechanisms. The most serious threat to science under peer review is a conservatism in which the safe squeezes out the novel. A look at the history of NIH involvement in DNA sequencing illustrates how a DARPA-like mechanism might prove more effective than external, prospective peer review. In 1981, Leroy Hood and his colleagues at Caltech applied for NIH (and NSF) funding to support their efforts to automate DNA sequencing. They were turned down. Fortunately, the Weingart Institute supported the initial work that became the foundation for what is now the dominant DNA sequencing instrument on the market. By 1984, progress was sufficient to garner NSF funds that led to a prototype instrument two years later. In 1989, the newly created National Center for Human Genome Research (NCHGR) at NIH held a peer-reviewed competition for large-scale DNA sequencing. It took roughly a year to frame and announce this effort and another year to review the proposals and make final funding decisions—a long time in a fast-moving field. NCHGR wound up funding a proposal to use decade-old technology and an army of graduate students but rejected proposals by J. Craig Venter and Leroy Hood to do automated sequencing. Venter went on to found the privately funded Institute for Genomic Research that has successfully sequenced the entire genomes of three microorganisms and has conducted many other successful sequencing efforts; Hood's groups, first at Caltech and then at the University of Washington, went on to sequence the T cell receptor region, among the largest contiguously sequenced expanses of human DNA. Meanwhile, the

army of graduate students has yet to complete its sequencing of the bacterium *Escherichia coli*. The point is not that the study section bet wrong—any research funding must be fault-tolerant and take risks—but that it bet on old technology over new.

NIH and NSF have long struggled with the tendency toward conservatism in peer review. NSF has set aside small grants for exploratory research subject only to expeditious staff review. With NSF's tradition of grant managers rotating into and out of their fields in academe, this is similar in spirit to DARPA, although the dollar amounts are generally too small to fund more than pilot projects. NSF has a good idea, but there is no reason to believe that innovative projects are always small. Besides, imposing a requirement that innovation prove itself early in small grants runs the risk of prematurely declaring failure and forcing investigators to write a follow-up grant at the same time that they have only a few months funding to do the pilot work. At NIH, some study sections set aside specific grants or are given the option of selecting out one or a few especially novel proposals for special consideration. But this does not avoid the inefficiencies of group process and grant-proposal preparation, and it ultimately amounts to a few groups doing sporadically what individual experts might do better.

A small dose of DARPA

A DARPA-like funding mechanism cannot cover the same breadth of science and technology as NIH or NSF. Even if a pilot test of a DARPA-like program is a success, it still should be considered as an alternative for a few select programs only. Much of the most important work supported by NIH and NSF is conducted through tens of thousands of relatively small grants. Innovation bubbles up in unexpected places thanks to the flexibility of the grant mechanism, which leaves funds largely in control of investigators. NIH handles 45,000 grant applications per year. It would be folly to adopt DARPA's methods for so many small projects covering enormous areas of science. The DARPA system cannot scale up easily, because its effectiveness depends on a flat bureaucracy and strong direct accountability from manager to agency director. The DARPA process is best suited to force scientific and technical progress in critical areas and to accomplish tasks when a new technology is promising but not yet proven. It is not suited to sustaining the bulk of science.

DARPA-like pilot projects might be tried first by one or a few NIH institute or center directors working with their respective councils to foster specific fields or to develop needed technical capacities. If NIH were to experiment with a DARPA-like mechanism, it should focus on areas ripe for such experimentation, such as:

- An emerging technological capacity that would be widely beneficial if successfully developed,
- An advance promising a major leap, not an incremental improvement.
- A capacity whose development requires substantial sustained funding,
- A field or technique unlikely to be developed by ongoing academic efforts or within industrial firms,
- An emerging scientific field or technical area that lacks a natural disciplinary base, or
- A promising new field populated by only a few individuals.

NIH has amply demonstrated its agility and excellence in maintaining scientific quality and administering a credible and effective process for allocating funds. That solid base of peer-reviewed science should be not be chipped and fragmented. The edifice could benefit from a new wing, however, that poses little danger to its foundations. One or two institute directors could hire some rising stars and make them responsible for moving their fields ahead rapidly. After four or five years, the results of NIH's "DARPA corps" could be compared to the record of peer review groups in similar areas.

Testing a DARPA mechanism within NIH is not a call to end peer review as we know it, or even a substantial fraction of it. But neither is the generally excellent track record of NIH and NSF any proof that a DARPA-like mechanism can't improve the system. In the 1960s, C. Jackson Grayson wrote a classic work on oil drilling that demonstrated why a long-term, diversified strategy is important for success when confronting uncertainty. Peer review is best regarded as a way to contend with moderate uncertainty, but it is not a good way to decide where to wildcat. DARPA's methods seem better suited to that, and some wildcatting is a good idea.